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EXPLANATORY MODELS FOR NEUROPLASTICITY IN RETINOTECTAL CONNECTIONS

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There has been a certain amount of controversy and confusion of late in the literature that deals with the growth and maintenance of retinotectal connections. In brief, the original explanatory model advanced back in the early 1940's is now being questioned by a number of people in the light of some new and apparently conflicting findings, creating a situation that now prompts us to undertake some further experiments.

First by way of background, the eye and the brain of the goldfish on which much of the work has been done, shown in Figure 1, is a relatively

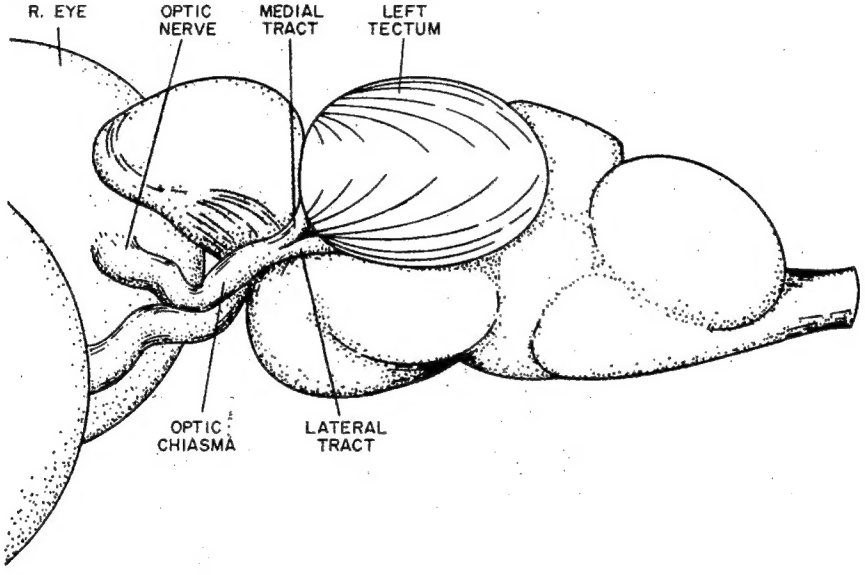

Figure 1. A drawing of the brain of the common goldfish, Carassius auratus, with the retinotectal system shown in white. Each optic nerve completely crosses at the chiasm and divides into two brachia which run along the medial and lateral tectal margins sending off fascicles of fibers in the directions indicated by the black lines.

simple system in which nerve fibers arising from cell bodies in the retinal layer of the eye grow centrally to connect directly in topographical fashion with the optic lobe or tectum of the mid-brain on the opposite side.

The earlier work of Attardi and Sperry (1963) summarized in Figure 2 shows the types of growth

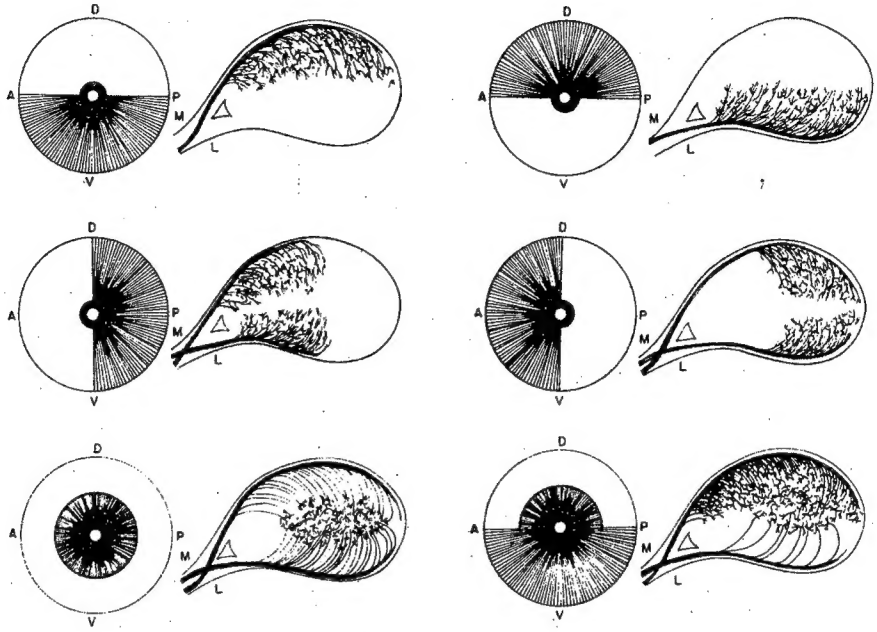

Figure 2. Diagrammatic reconstructions of regeneration patterns formed in optic tracts and tectum by fibers originating in different retinal halves, as indicated (After Attardi and Sperry 1963).

patterns, seen with a modified Bodian stain selective for regenerating fibers, that were obtained from different sectors of retinal field when the rest of the retina was removed. This illustrates the main point at issue: namely the conclusion that fibers of the optic nerve grow selectively along specific routes to reach specific target points in the tectum, to establish thereby an orderly topographic map of the retinal field on this brain center.

This same kind of orderly mapping is found in the initial development in the embryo and also in regeneration in the adult amphibian or fish when the nerves are divided and the hundreds of thousands of fibers scrambled (Sperry 1943; 1944; 1948). The scrambled fibers somehow unsort themselves and regrow the appropriate topographic connections required for optokinetic, orienting and visual discrimination behavior. The more recent techniques of microelectrode mapping of the visual field (Cronly-Dillon 1968; Gaze 1959; Jacobson and Gaze 1965; Maturana *et al*. 1959) and Nauta degeneration stains suitable for fish (Roth 1972) confirm in general these earlier observations of selective optic nerve growth. The same holds even when the eye is rotated or inverted so that the animals are obliged to view everything upside down and backward after regeneration (Sperry 1943; 1944) and also when the nerves are crossed to the wrong side of the brain, producing a left-right reversal in visual perception (Sperry 1945). These maladaptations in visual orientation remain uncorrected by experience.

It was concluded from these and related findings that each retinal point is pre-programmed to connect with a corresponding complimentary point in the tectum. It was inferred that the nerve cells of the retina and tectum must acquire cell-unique cytochemical tags that serve as markers to identify each cell and its fiber according to the precise location of the cell body within the retina or tectum. Each locus in the retina was inferred further to have a corresponding complimentary or matching locus in the tectum for which it possesses a selective preferential chemical affinity or selective adhesivity (Sperry 1943; 1944; 1945; 1951; 1965).

This kind of refined chemical labeling of hundreds of thousands of individual cells in an adult tissue seemingly homogeneous in appearance was a bit hard to accept back in early days, and apparently still is in some places. It was suggested (Sperry 1945; 1951; 1963) that such chemical labeling could easily be brought about by a polarized field-like or gradient type of differentiation on at least two, perhaps three axes in the developing retinal and tectal fields. The

latitude and longitude of each cell, so to speak, becomes stamped on the cell in some chemical form.

The same scheme will work and is assumed to apply also to the visual system of higher forms (Sperry 1963) and also to other systems like the vestibular system and the cutaneous system where we have the same kinds of gradients and topographic mapping on the brain centers (Sperry 1951). In other words, this retino-tectal model and the points that are at issue here involve general principles that have wide applicability to the formation of nerve connections throughout the nervous system.

We can now consider some of the subsequent seemingly discrepant findings that have been obtained largely by Gaze and his associates, by Sharma, by Yoon, and others. Compound eyes (Figure 3) formed experimentally in the early amphibian

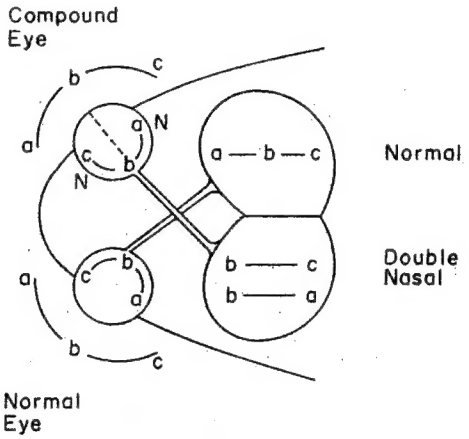

Figure 3. Diagram of the visual field to retina to tectum projection in Xenopus with a double nasal compound eye.

embryo by uniting two nasal half retinas or two temporal halves come to project not to just the corresponding half of the tectum but to the whole tectum, each half spreading across the entire tectum in a mirror image pattern (Gaze *et al.* 1965; Straznicky *et al.* 1971). In goldfish (Figure 4), when the posterior half of the tectum is removed, it is reported that the whole retina in time will

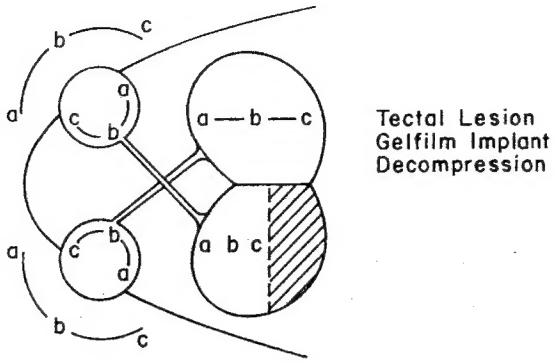

Figure 4. Diagram of the visual field to retina' to tectum projection in a goldfish with either a caudal tectal ablation or a mechanical barrier inserted along the dotted line.

come to project in an apparently orderly but compressed pattern upon the remaining half tectum (Gaze and Sharma 1970) and this can occur under conditions where regeneration of tectal cells appears unlikely (Yoon 1971). A gelfilm implant separating rostral and caudal tecta induces a similar compression followed by expansion over the entire tectum after absorption of the gelfilm (Yoon 1972a). This must involve a considerable rearrangement of retino-tectal connections throughout the whole remaining tectal half field. Similarly, as illustrated in Figure 5, it is reported that when half of the retina is removed and sufficient time is allowed, that the remaining half retina will expand its projection to effect an orderly coverage of the whole extent of the tectal field (Horder 1971; Yoon 1972b). Again this would involve a considerable reorganization of the original pattern of retino-tectal connections.

These and similar findings have been taken to mean by a number of investigators (Gaze 1970; Gaze and Keating 1972; Gaze and Sharma 1970; Sharma 1972a; Straznicky *et al.* 1971) that the old explanatory model is not quite adequate and Gaze (Gaze 1970; Gaze and Keating 1972) proposes a modified hypothesis. This would retain the concept of gradients and of chemical ordering, but the

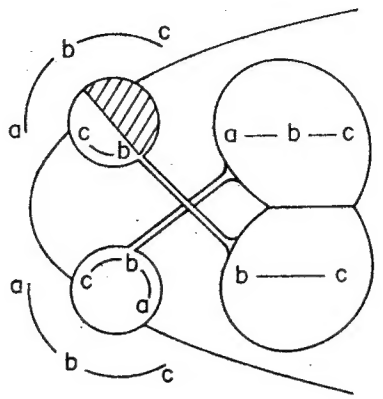

Figure 5. Diagram of the visual field to retina to tectum projection in a goldfish sustaining a temporal retinectomy.

optic fibers instead of finding predetermined targets are hypothesized to arrange themselves in the course of growth in an orderly way and on a competitive basis to fill up whatever gradient is available, establishing their connections on a kind of sliding scale, instead of one that is prefixed.

Assuming these findings hold up, our own interpretation has been that these apparent discrepancies are not necessarily in conflict at all, but are readily and better accounted for in terms of the original model than in terms of the sliding scale concept (Sperry 1965; Meyer and Sperry 1973). The polarized field-like retinal or tectal differentiation system on which the original explanation was based is almost by definition as a morphogenetic field (Weiss 1939), something which if cut in half will automatically regulate itself into a whole.

Thus the compound eyes, formed in the early stages of growth and development may be assumed, by the time testing occurs, to no longer contain two half retinas as supposed, but rather two whole twin retinal fields. This would explain why the two nasal or temporal halves overlap across the

whole tectum in mirror image alignment. Similar surgical manipulations on the developing limb bud are known to produce the growth of duplicate limbs (Weiss 1939; Saunders and Gasseling 1968). Similarly after removal of the half tectum or retina in the goldfish, it is possible that there is still sufficient developmental plasticity so that the remaining half field of the tectum or retina regulates into a whole field and changes accordingly the chemical labels for cell localization. Recent experiments (Sharma and Gaze 1971; Yoon 1973) suggest that this regulative plasticity with respect to compression and expansion may persist after the capacity for reversal of polarity is lost. Goldfish of the size used are still growing rapidly and the retinotectal system appears to be still growing by cell division (Kirsche and Kirsche 1961).

In other words, the observed plasticity in these experiments is not, in our view, a plasticity in the process by which nerves grow and form their connections. Instead the plasticity is in the precursor process by which the nerve cells differentiate and acquire their local chemical tags. The plasticity that is, is in the organizational dynamics of the developing morphogenetic fields.

We have recently attempted a critical test between these alternatives in a system in which tectal growth is complete and regulation therefore improbable (Meyer and Sperry 1973). In the tree frog *Hyla regilla* tectal growth by cell addition appears to end by metamorphosis (Larsell 1929; Straznicky and Gaze 1972), and if our view is correct, one would not predict these same kinds of plasticity or "sliding scale" effects to obtain in this adult animal. Repeating the procedures used in some of the previous experiments, the posterior half of the tectum was ablated and in many cases the optic nerve was divided and allowed to regenerate. As indicated in Figure 6, if the model of Gaze is correct, one would expect to eventually get a compression of the whole retina onto the remaining front half of the tectum. According to the original model, on the other hand, one would expect to find no such compression and that the scotoma or blind area would remain unchanged.

The results both electrophysiological and

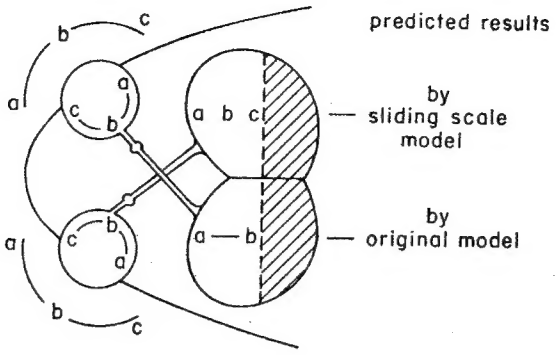

Figure 6. Predicted retinotectal projection patterns of the adult frog following caudal tectal ablation and optic nerve crush.

behavioral were clearly in favor of the original hypothesis. The behavioral data were based on a perimetry technique for which these animals are well suited. Like most anurans *Hyla* are typically quiescent but readily orient to potential food objects moving in their visual field. By aligning a calibrated glass hemisphere over a frog resting on a table top, visual stimuli could be presented near the glass surface to precise locations in the visual field. In practice this was done by blinding the right visual field by an optic nerve crush. From the blind area a 1-4° black disc mounted on a glass rod was slowly advanced into the left posterior field. At some point this typically produced a sudden turning of head and body toward the stimulus. By this procedure the temporal contour of the left visual field from the horizon to 50° upwards could be mapped with an accuracy of about 10°.

Figure 7A shows such a contour indicated by the front edge of the stippling obtained from a normal animal. The superior field is, as expected, quite large extending in parts to 180° behind the frog. After a caudal right half tectum ablation this field contour regresses to near the 60° meridian. Considering the 55-60° optic axis divergence from the midline, this represents an approximate half field scotoma. This is illustrated in Figure 7B, in the map of an animal which sustained this

surgery 7 to 10 days prior. Figure 7C shows this same animal remapped 124 days after surgery, a time more than sufficient for the elimination of the scotoma in goldfish. The extent of the field is found not significantly altered.

Three other animals with both complete maps also showed an essentially unchanged scotoma. In addition, there was a small region at the temporal extreme, shown on the figure by the circled numbers, from which false counterreversal responses to the mirror image position could be obtained. Previous work has shown that optic fibers terminating on the wrong tectum mediate these responses (Sperry 1945). Thus fibers corresponding to the ablated tectum appear to grow out of their usual course all the way to the appropriate region of the contralateral tectum rather than terminate in the inappropriate rostral tectum. This presence of alternative correct sites, however, is not the reason for the absence of field expansion since, as will be described, this also fails to occur after bilateral ablations.

The electrophysiological unit recording results obtained with a method similar to Gaze's (1959) also demonstrate the apparent permanency of these scotomas. In Figure 8A is seen a map of the left superior visual field onto the dorsal right tectum of a normal animal. The numbers and letters indicate corresponding electrode placements and receptive field positions, a measure of the respective optic axon terminal and ganglion cell locations (Gaze 1958; Lettvin *et al.* 1960). The retinotectal projection pattern obtained is similar to that reported for other frogs (Gaze 1958; Jacobson 1962). After an optic nerve crush this same organization could again be recorded as early as 60 days postoperatively. Electrophysiological maps were obtained from 9 animals with right caudal tectal ablations and from 4 with bilateral ablations combined in most cases with optic nerve section. In contrast to goldfish where the scotoma vanishes only 90 days after this surgery (Yoon 1971), the blind area remained essentially unaltered up to 339 days after tectal ablation. The longest surviving animal, shown in Figure 8B, demonstrates a typical scotoma of the appropriate size and location. Other scotomas produced by

mid tectal ablations were preserved, contrary to the case in goldfish (Sharma 1972a), up to 171 days in the four animals measured. A map illustrated in Figure 8C from one of these frogs 106 days after the ablation and left optic nerve section shows the missing retinal representation. Similarly in 3 other animals medio-laterally oriented pieces of gelatin film implanted into the tectum failed to induce the fiber compression reported in goldfish despite survival periods of up to 291 days. Thus both the electrophysiological results and the behavioral data appear to rule out the "sliding scale" model.

Very recently Straznicky (1973) has demonstrated a similar lack of plasticity in the adult *Xenopus* using electrophysiological measurements subsequent to various unilateral tectal ablations, and Gaze (1970) has previously reported these kinds of results after similar lesions in the late tadpole stages. We might also add that in the chick embryo DeLong and Coulombre (1965) and later Kelly (1970) have shown that optic axons from surgically reduced retinas grow only to the appropriate tectal regions leaving the inappropriate regions uninnervated. The apparent plasticity shown in the *Xenopus* compound eye experiments almost certainly involves regulative type changes in the locus specificity properties of retinal neurons and in reality these experiments also conform to the idea of selective innervation. The recent compound eye results of Hunt and

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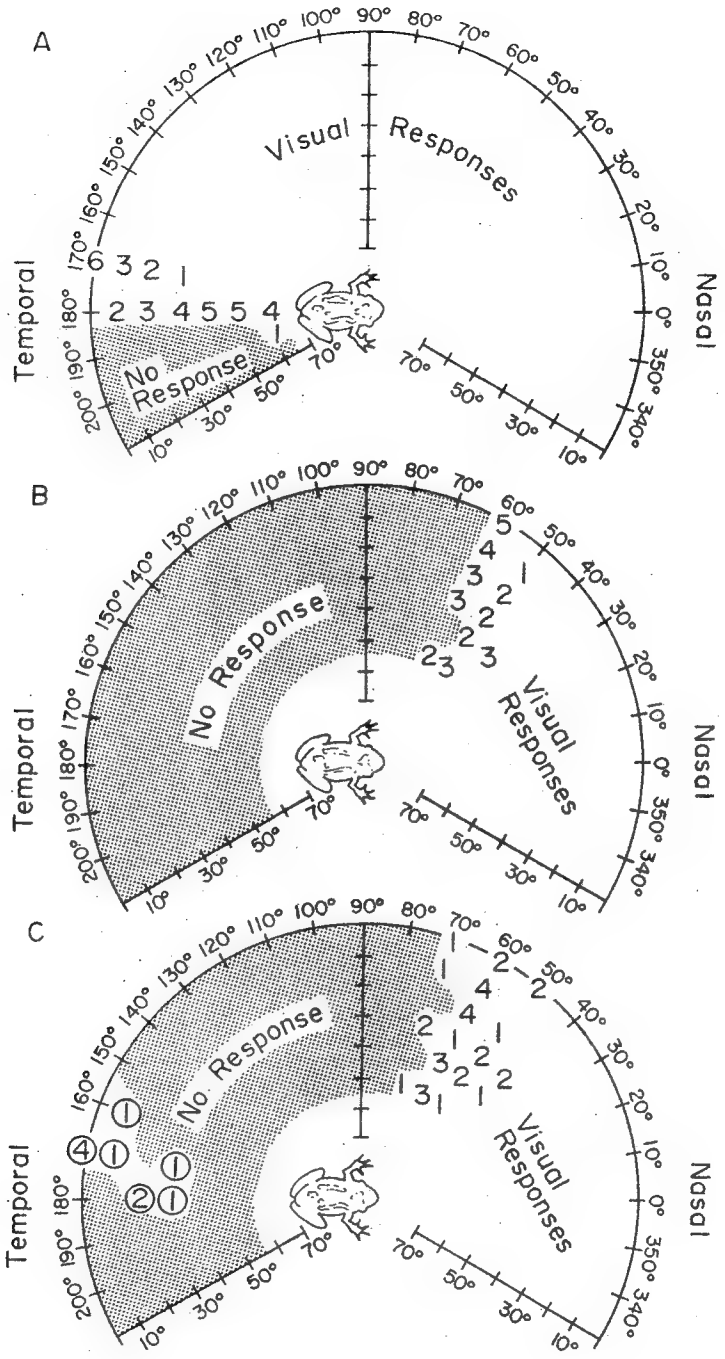
Figure 7. Behaviorally obtained maps showing the posterior contour of left visual space. The stimulus was advanced in a temporal nasal direction along each tested 10° parallel until an orienting response was obtained. The number of responses at each position is shown and the stippling indicates the visual field giving no responses. The right eye was blinded by nerve interruption in all cases. A. Normal. B. Frog with right caudal half tectum ablation sustained 7-10 days prior. C. Same animal as in B but tested 124 days after tectal surgery. Circled numbers represent contralateral orientation movements to the mirror image position.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Jacobson (1973) directly supported the same interpretation.

Firm inferences about neuroplasticity and regulation in the goldfish, however, are hindered by some apparent inconsistencies in the goldfish work and by an absence of critical experiments. There is disturbing lack of agreement between the electrophysiological data on which all of the evidence for plasticity rests and the correlated anatomical data. Yoon (1972b) and Horder (1971) both report electrical evidence for uniform spreading of a surgically formed half retina over an entire normal tectum. In contradiction to this, the original study of Attardi and Sperry (1963) using Bodian staining, Roth's (1972) recent similar work, and our own autoradiography experiments (Meyer 1973a) show that these same half retinas preferentially terminate in the appropriate tectal region even after long survival periods. Yoon (1972d) and Horder (1971) have further electrophysiological data apparently showing that if noncomplimentary retinal and tectal halves are removed, the remaining retina spreads over the entire inappropriate half tectum. Under these same conditions the anatomical evidence of Roth (1972) indicates that innervation is restricted to the region near the lesion leaving much of the tectum without optic fibers.

Worse yet, the electrophysiological evidence seems self-contradictory. While Yoon (1972b) claims both nasal and temporal hemiretinas show plasticity, Horder (1971) has evidence that only a nasal half retina expands in this manner and Jacobson and Gaze (1965) have data suggesting neither half does this. Although only a rough

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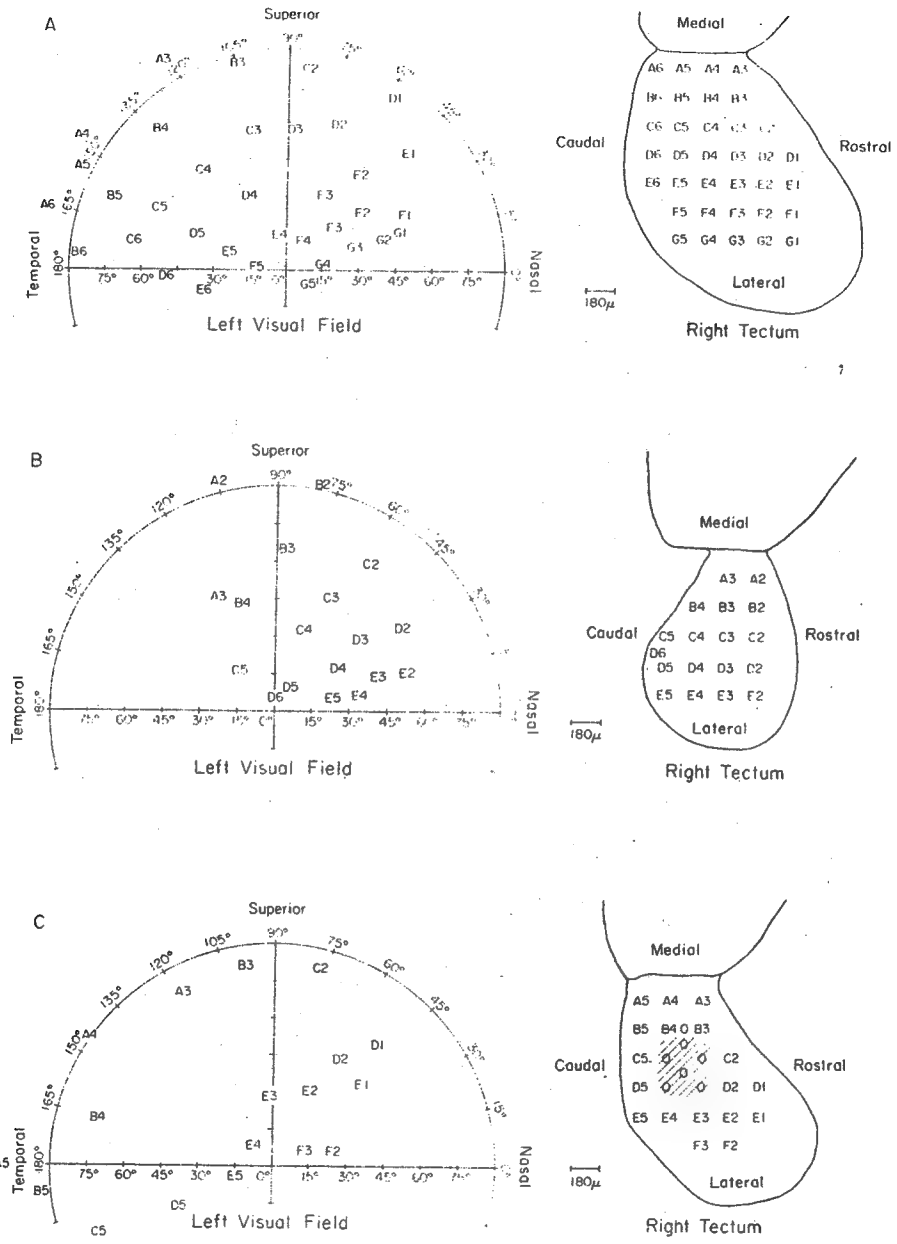
Figure 8. Electrophysiological map of left visual space onto right tectum with numbers and letters indicating corresponding electrode placements and receptive field location. A. Normal. B. Right caudal half tectum ablation and left optic nerve crush 339 days prior. C. Ablation of a rectangular piece of dorsal right tectum and left optic crush 106 days prior. Crosshatching indicates pia covered ablation area with o indicating electrode positions giving no responses.

mediolateral incision is sufficient to induce complete field compression onto the rostral tectum in Yoon's hands (1971), a similarly placed even larger lesion does not produce this result in Sharma's (1972b) experiment. Medial or lateral tectal ablations have been reported not to cause plasticity (Gaze and Jacobson 1965) and the thought that this may be a consequence of interference with the medial optic tract is supported by Yoon (1971). Yet after removal of rostral tectum causing comparable tract damage, a compressed visual field representation onto caudal tectum is nevertheless found, according to Sharma (1972b). In the original Gaze and Sharma (1970) study simple removal of caudal tectum invariably resulted in tectal positions from which two widely separated receptive fields could be recorded. Not one instance of this field reduplication was found by Yoon (1971).

Many of these apparently conflicting electrophysiological results may very possibly be accounted for by differences in postoperative survival periods or subtle surgical variables. However, there is as yet no direct evidence or convincing arguments that would resolve these discrepancies. In the additional light of the chick, adult frog, and goldfish anatomical investigations all showing selective innervation, one may perhaps question whether some of these goldfish electrophysiological experiments accurately describe the distribution of optic axon terminals on the tectum. The recordings from goldfish with retinal lesions, at variance with anatomical results, would seem particularly suspect because of possible optic aberrations, changes in retinal topography, and regeneration of new retina consequent to surgery. While the electrical measurements following tectal lesions would seem to indicate some genuine change in fiber distribution, better techniques may be called for. We have recently employed a more refined electrophysiological method recording with the eye under water instead of in air, as previously done, and with more precise electrode placement and eye alignment techniques (Meyer 1973b). Initial results raise in our minds the possibility that some measurement errors may exist in previous work. Whatever is the case, it seems to us that the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goldfish electrophysiology work showing plasticity needs further analysis and some validation of the inferred fiber distribution and connectivity pattern by anatomical behavioral or postsynaptic recording methods.

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